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EXAMINER	
LUCAS, ZACHARIAH	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 11/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,709	SIPPEL ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2004 and 05 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,24 and 26-83* is/are pending in the application.

4a) Of the above claim(s) *37,38,45,46,48-59 and 61-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,24,26-36,39-44,47,60 and 74-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Currently, claims 1, and 24, and 26-83 are pending in the application.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's Responses filed on September 3, and October 5, 2004 have been entered.

3. In the prior action, mailed on April 5, 2004, claims 1 and 24-83 were pending. Claims 25, 37, 38, 45, 46, 48-59, 61-73, 82, and 83 were withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions. Claims 1, 24, 26-36, 39-44, 47, 60, and 74-81 were rejected. In the Responses, the Applicant cancelled claims 25; and amended claims 1, 30-32, 34-36, 39-41, 43-44, 59, 80, and 81.

4. It is noted that previously the Applicant had elected embodiments of the claimed inventions wherein the adaptor polypeptide is a protein capable of binding to the alpha subunit of a G-protein. In filing the RCE, and with the consent of the Office, the Applicant has amended the claims to read on embodiments wherein the adaptor protein is a Grb2 polypeptide, and so as to exclude the previously elected embodiments.

Thus, the elected inventions of the current application are drawn to cells comprising a membrane receptor and a fusion protein comprising an effector polypeptide fused to an adaptor polypeptides, and methods of using such in an assay for determining the suitability of a test

substance as a ligand for the receptor by contacting the cells with the substance wherein the receptor may activate a signal pathway when a ligand binds the receptor. In particular, the Applicant has elected embodiments wherein the receptor is an epidermal growth factor (EGF) receptor, the effector polypeptide is a Ras polypeptide, the adaptor polypeptide is Grb2, and to embodiments wherein the detection step of the claimed methods involve the detection of the expression of a reporter gene in the cell.

In view of the shift of the elected inventions, previously withdrawn claims 82 and 83 are rejoined to the elected claims.

5. Claims 1, 24, 26-36, 39-44, 47, 60, and 74-83 are under consideration.

Claims 37, 38, 45, 46, 48-59, 61-73 are withdrawn as to non-elected inventions.

Specification

6. **(Prior Objection- Maintained)** In the prior action, the specification was objected for lacking the section s required by #7 CFR 1.77. While the guidelines suggested in the prior action need not be followed, the Applicant is required under 37 CFR 1.74 to include in the specification a Brief Description of the Figures. Because no such section of the specification has been provided, the objection is maintained.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. **(New Rejection)** Claims 1, 24, 26, 27, 30-34, 60, 74-83 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. These claims read on transformed cells. However, these claims do not require that the cells be isolated, and therefore include embodiments wherein the cell is part of, or inside of a human being. It is suggested that the claims be amended to read on - - An isolated transformed cell- -.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. **(New Rejection)** Claim 60 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim refers to a kit for use in the assay of claim 35 "which comprises cells as claimed in claim 35." However, as indicated in the earlier part of the rejected claim, claim 35 is directed to (i.e. claims) an assay, and does not claim a cell. It is suggested that claim 60 be amended to describe in words the cells to be included in the kit (i.e. incorporate the language of claims 1 and 30).

Clarification is required.

11. **(New Rejection)** Claim 79 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim purports to further limit the cells of claim 1 to embodiments wherein "the membrane receptor is the human epidermal growth receptor." However, claim 1 is drawn to cells comprising a human epidermal growth receptor. It is

therefore unclear how the scope of the cells of claim 79 is different from the scope of cells in claim 1.

Clarification is required.

12. **(Prior Rejection- Withdrawn)** Claims 30-36, 39-44, 47, and 60 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite because it is not clear what pathways are included by the phrase "Ras-like." In view of the amendment of the claims, such that they no longer refer to Ras-like signal pathways, the rejection is withdrawn.

13. **(Prior Rejection- Withdrawn)** Claims 30-36, 39-44, 47, and 60 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In view of the amendment of the claims, the rejection is withdrawn.

(Prior Rejection- Withdrawn) Claim 41 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The arguments in traversal were persuasive, the rejection is therefore withdrawn.

14. **(Prior Rejection- Withdrawn)** Claims 1, 24, 26-36, 39-44, 47, 60, 74-78, 80, and 81 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite because it is unclear what receptors fell within the claim language "a human epidermal growth factor type membrane receptor." In view of the amendment of the claims such that they refer to epidermal growth factor receptor membrane receptors, the rejection is withdrawn.

15. **(Prior Rejection- Withdrawn)** Claims 80 and 81 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite because it was unclear what was meant by the phrase "wherein the fusion protein is coded for a nucleic acid. In view of the amendment of the claims clarifying that the fusion protein is encoded "by" the nucleic acid, the rejection is withdrawn.

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. **(Prior Rejection- Withdrawn)** Claims 1, 24, 26, 27-36, 39-44, 47, 60, 74-78, 80, and 81were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for recombinant cells wherein the Applicant has inserted a heterogeneous receptor into the cell, does not reasonably provide enablement for cells wherein the inserted receptors comprise portions of two or more receptors (e.g. the ligand binding domain of one receptor, and the transmembrane/cytoplasmic domain of another). In view of the amendment of the claims to read on cells comprising a "human epidermal growth factor membrane receptor," the rejection is withdrawn.

18. **(Prior Rejections- Withdrawn)** Claims 1, 24, 26-31, 34-36, 39-44, 47, 60, and 74-81 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain cells and assays does not reasonably provide enablement for the elected invention wherein the receptor is a tyrosine kinase receptor, or to embodiments wherein the receptors' mediator section is associated with any tyrosine kinase, and the adaptor protein is a

protein capable of binding an alpha unit of a G-protein (a Gα protein). These claims were also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for reading on the same claimed inventions. In view of the amendment of the claims such that they no longer read on the rejected embodiments, the rejection is withdrawn. .

19. **(Prior Rejection- Withdrawn)** Claims 1, 24, 26-36, 39-44, 47, 60, 74-78, 80, and 81 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims were rejected because there was insufficient written description support for the genus of inventions comprising human epidermal growth factor (EGF) *type* receptor effector domains. In view of the amendment of the claims such that they now read on inventions comprising the effector domain of an EGF receptor, the rejection is withdrawn.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. **(Prior Rejection- Restated and Maintained)** Claims 1, 24, 26, 27, 30-33, 35, 36, 39-44, 47, 60, 74, 75, and 77-81 were rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart as applied to claims 1 and 30 (and others) above, and further in view of Ostanin et al. (U.S. Patent 6,251,605), Isakoff et al. (EMBO J 17(18): 5374-87), and Aronheim (Nuc Acids

Res 25(16): 3373-74), and further in view of Li et al. (J Biol Chem 272(16): 10337-10340) and Baldari et al. (J Biol Chem 267(7): 4289-91). This rejection is restated such that claims 1, 24, 26, 27, 30-33, 35, 36, 39-44, 47, 60, 74, 75, and 77-81 are rejected as obvious under 35 U.S.C. 103(a) over the teachings of Trueheart (U.S. Patent 6,159,705) and Ostanin, in view of Isakoff, Aronheim, and Li, and further in view of Suen et al. (Molec Cell Bol 13:5500-12). The claims have been amended to read on the claimed inventions wherein the receptor is an EGF receptor, and the adaptor polypeptide in the fusion protein is a Grb2 polypeptide.

The Applicant traverses this rejection on two grounds. First, the Applicant argues that the "generic disclosure in the Trueheart patent is being used to impermissibly reconstruct the claimed invention." The Applicant argues that an example of the impermissible use of this reference is its use in combination with the teachings of Aronheim and Isakoff, which do not teach the use of the EGF receptor. The Applicant argues that there would have been no motivation to combine these references to arrive at the claimed invention, and that the systems in these references are not analogous. The second argument in traversal is that the claims have been amended to include the limitations of claim 25 (now cancelled), which was not previously rejected. The previously withdrawn limitation is the requirement that the adaptor polypeptide is a Grb2 polypeptide.

The first argument in traversal is not found persuasive. It is not clear what the Applicant means by indicating that the use of the Trueheart reference was impermissible, so it is assumed that the basis of the Applicant's argument is that there is no motivation to combine the teachings of the cited references.

The teachings of the references were described in the prior actions. In particular, Trueheart was described as teaching the following:

> The patent teaches that, where a heterologous receptor is provided, the preferred embodiment also includes the inactivation of the homologous receptor (native to the cell). Col. 15, lines 13-15. Further, the reference teaches that the host cells for the heterogeneous receptor are cells wherein the receptor can activate a signal transduction pathway. Col. 15, lines 60-63. As an example of such a pathway, the patent discusses the yeast Ras pathway. Col. 16, lines 30-52.

Thus, the patent teaches the insertion of the heterologous receptors into the yeast cell such that they can activate the Ras signal transduction pathway. Each of Isakoff and Aronheim teaches the use of fusion proteins as adaptors to bypass deficiencies in cellular pathways, and indicate that what is necessary for the activated Ras to signal its pathway is for the protein to localize the Ras to the plasma membrane. See e.g., Aronheim, page 3373 left column. In view of these teachings, it would have been obvious to those in the art that fusion of activated Ras to any compound that would localize the pathway inducer to the cellular membrane would be effective in activating the Ras pathway. Because Trueheart teaches the expression of heterologous receptors and the incorporation of such receptors into endogenous pathways, and particularly the Ras pathway, and because the Isakoff and Aronheim references teach methods of incorporating signals otherwise excluded from cellular pathways into the cell signal transduction pathways, it would have been obvious to those in the art to use fusion proteins such a those taught in these two references to incorporate the heterologous receptors of Trueheart into the yeast cell signal pathways

The Applicant has asserted that the teachings of Isakoff and Aronheim are not teachings in an analogous art. Analogous art is art "in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned," or "even though it may be in a different field from that of the inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's

attention in considering his problem." See, MPEP § 2141.01(a) (quoting, respectively, In re Oetiker, 24, USPQ2d 1443, 1445 (Fed. Cir. 1992); and In re Clay, 23 USPQ2d 1058, 1060-61 (Fed. Cir. 1992). From this description of the teachings above, it is apparent that the teachings of the Isakoff and Aronheim references, in teaching the incorporation of an isolated receptor into the biological systems of a cell, would have been teachings relevant to the problem being solved by those in the art of Trueheart and the present application; i.e. art relating to the inclusion of heterologous receptors into the biological systems of cells. The Applicant's assertions that the teachings of the Aronheim and Isakoff references are non-analogous are therefore not found persuasive.

Additionally, while the teachings of Aronheim and Isakoff do not specifically teach the fusion of Grb2 or the targeting of such adaptor fusion polypeptides to the EGF receptors, the cumulative teachings of these two references indicate that the adaptor fusions may be used to target Ras to other desired cell membrane targets. This, in combination with the teachings of Trueheart, which suggests the EGF receptor as the heterologous target against which ligands can be identified in the suggested system (e.g. column 23, lines 24-60), would have rendered it obvious to those in the art to adapted the fusion protein to target activated Ras to the heterologous EGF receptor.

With respect to the argument that the claims have been amended to incorporate the limitations of claim 25, and that this claim was not previously rejected, it is noted that this claim was not previously rejected because the claim was withdrawn from consideration. Thus, the addition of this limitation does not per se avoid the prior rejection. It is however noted that, while

the references do suggest the other limitations of the claims, they do not appear to suggest the use of Grb2 as the adaptor polypeptide without additional teachings.

However, the art is replete with teachings that Grb2 is an adaptor protein that binds to the EGF receptor. The teachings of Suen, which have been incorporated into the rejection, render obvious the use of Grb2 to interact with EGF receptors so as to incorporate them into a Ras pathway (which was suggested in the art as described in the prior actions) by which the test ligands interaction with the receptor may be detected. See, Suen, abstract (teaching that the activated EGF receptors bind to Grb2). See also, Rozakis-Adcock (Nature 363:83-85-providing teachings supporting those of Suen). In view of this, it would have been obvious to those in the art to use fusion proteins comprising activated Ras and Grb2 as the adaptor fusion proteins that may be used to detect interaction between the test ligands and the heterologously expressed EGF receptor.

In view of the revised rejection, this argument in traversal is therefore not found persuasive.

22. **(Prior Rejection- Withdrawn)** Claims 1, 2, 6, 9, 18-21, 26, 27, 31-33, 35, 36, 42, 43, 44, 47, and 60 were rejected under 35 U.S.C. 103(a) as obvious over Trueheart in view of Ostanin, Isakoff, Aronheim, Li, and Baldari as applied against claim 31 above, and further in view of Pacifici et al., WO 94/29458 (Se also U.S. Patent 5,521,295). In view of the amendment of the claims so as to exclude hybrid receptors, this rejection is withdrawn as redundant.

23. **(Prior Rejection- Restated and Maintained)** Claim 34 was rejected in the prior action under 35 U.S.C. 103(a) as obvious over Trueheart in view of Ostanin, Isakoff, Aronheim, Li, and Baldari as applied against claim 31 above, and further in view of Mitsuzawa et al. (Genetics 123: 739-48), and DeClue et al. (Mol Cell Biol 11(6): 3132-38). The rejection is now revised such that the claims are rejected over the teachings of Trueheart, Ostanin, Isakoff, Aronheim, Li, and Suen, further in view of Mitsuzawa and DeClue. The Applicant has provided no arguments in traversal of this rejection other than those presented above. Because those arguments are not found persuasive, the rejection is maintained for the reasons above, and the reasons of record.

24. **(Prior Rejection- Withdrawn)** 1, 24, 26, 27, 30-36, 39-44, 47, 60, 74, 75, and 77-81 were rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart, Ostanin, Isakoff, Aronheim, Li, Baldari, Mitsuzawa, and DeClue as applied above, and further in view of either Jiang et al. (Nature 395: 808-13), or Bence et al. (Nature 289: 296-99) and in light of the teachings of Kawakami et al. (J Immunol 16: 1785-802), and Rawlings et al. (Science 271: 822-825). This rejection was based on embodiments wherein the receptor is, or is associated with, a tyrosine kinase (the mediator), the adaptor is a protein capable of binding to an alpha subunit of a G-protein, and the effector is a Ras protein. In view of the amendment of the claims to exclude such embodiments, the rejection is withdrawn.

25. **(Prior Rejection- Restated and Maintained)** Claims 28 and 29 were rejected under 35 U.S.C. 103(a) as obvious over Trueheart in view of Ostanin, Isakoff, Aronheim, Li, and Baldari as applied against claim 1 above, and further in view of any of Ashby et al. (U.S. Patent

5,569,588) or Fink (U.S. Patent 5,532,157), and further in view of the Applicant's disclosure on pages 42, and 74. The rejection is now revised such that the claims are rejected over the teachings of Trueheart, Ostanin, Isakoff, Aronheim, Li, and Suen, further in view Ashby, Fink, and the Applicant's admissions in the specification. The Applicant has provided no arguments in traversal of this rejection other than those presented above. Because those arguments are not found persuasive, the rejection is maintained for the reasons above, and the reasons of record.

26. **(Prior Rejection- Restated and Maintained)** Claim 76 was rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart in view of Ostanin, Isakoff, Aronheim, Li, and Baldari as applied to claims 1, 24, 26, 27, 30-33, 35, 36, 39-44, 47, and 60, and extended to new claims 74, 75, 77-81 above, and further in view of Delorme et al., Appl Environ Microbiol 55(9): 2242-46. The rejection is now revised such that the claims are rejected over the teachings of Trueheart, Ostanin, Isakoff, Aronheim, Li, and Suen, further in view of Delorme. The Applicant has provided no arguments in traversal of this rejection other than those presented above. Because those arguments are not found persuasive, the rejection is maintained for the reasons above, and the reasons of record.

27. **(New Rejection)** Claims 82 and 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Trueheart, Ostanin, Isakoff, Aronheim, Li, and Suen as applied above, and further in view of the teachings of Hart et al. (Oncogene 14: 945-53). Claim 82 is directed to embodiments of the cells of claim 1 wherein the cell is a yeast cell, and the fusion protein comprises a constitutively active human ras polypeptide fused to a murine Grb2

polyprotein. Claim 83 further indicates that the ras protein lacks the CAAX box found in the wild-type ras protein.

In addition to the teachings described above, Suen teaches that the Grb2 proteins and homologues share a conserved structure. Page 5500. Additionally, the reference teaches the murine and human Grb2 proteins are identical except for a single substitution at position 154 of the protein. Page 5504. In addition, it is known in the art that the mammalian Grb2 protein is able to substitute for the homologous protein in C. elegans, which Suen teaches shares a lower percent identity than the human and mouse proteins. Schlessinger, TIBS 18:273-75, at 274. Because the art indicates that the Grb2 homologues may be substituted for each other, and because the art indicates that the human and murine Grb2 proteins are nearly exactly identical, it would have been obvious to those in the art that these two proteins were functional equivalents for each other, and could substituted in one for the other. Thus, it would have been obvious to those in the art to use the murine Grb2 polypeptide in the place of the human Grb2 polypeptide in the construction of the fusion proteins suggested by the teachings of the other references.

With respect to the additional limitations of claim 83, Hart teaches that activated Ras protein may, although it normally requires the CAAX box to for activity, that the box may be deleted where alternative means are provided to localize the activated protein to the plasma membrane. As described previously, the teachings of Isakoff and Aronheim demonstrate that the purpose of the fusion protein is to bring its components to the plasma membrane such that the active component (the effector polypeptide) can perform its function. Thus, the teachings of Hart, Aronheim, and Isakoff would have rendered obvious the use of an active ras lacking a CAAX box where the ras is fused to another polypeptide that would localize it to the EGF

receptor, of Trueheart. Those in the art would have had a reasonable expectation of success in the use of such a modified ras due to the teachings of Hart.

These claims are therefore rejected as obvious for the reasons applied against claims 1, 24, 26, 27, 30-33, 35, 36, 39-44, 47, 60, 74, 75, and 77-81, in combination with the reasons described immediately above.

Conclusion

28. No claims are allowed.

29. The following prior art references are made of record and considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

> Buss et al., Science 243: 1600-03. This reference teaches the making of an active version ras through the insertion of a leucine at position 31 in the amino acid sequence. The reference is considered redundant to the teachings of Li.
>
> Lemmon et al., JBC 269: 31563-58. This reference teaches that the SH2 domain of Grb2 is the domain that binds to the EGF receptor, and that this domain appears to act independently of the binding of the SH3 domains of Grb2 to the other target proteins in the ras activation cycle. Thus, this reference provides additional grounds for finding that those in the art would have had a reasonable expectation of success in the use of the Grb2 protein as an adaptor protein to bring activated ras to the plasma membrane in an EGF receptor mediated fashion.
>
> Willumsen et al., EMBO J, 3: 2581-85. This reference teaches that the ras CAAX box is required for ras activity in that the post-transalation modifications of this box result in the proteins localization to the plasma membrane. See e.g., pages 2581 and 2584. The teachings of this reference predate the teachings of the Hart reference applied above.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner

JAMES HOUSEL 11/29/04
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600